Original Article

Somatic Complaints Are Significantly Associated with Chronic Uninvestigated Dyspepsia and Its Symptoms: A Large Cross-sectional Population Based Study

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Background/Aims

Somatization may influence persistence and severity of symptoms in gastrointestinal diseases. Some studies suggest that somatization is associated with chronic uninvestigated dyspepsia (CUD); however, the association is unclear. We aimed to determine the association between the profiles of somatic complaints with CUD and its symptoms.

Methods

In a cross-sectional study conducted on 4763 Iranian adults, somatic complaints were assessed using a comprehensive 31-items questionnaire. Patients with CUD were identified by the Rome III diagnostic criteria. Profiles of somatic complaints were derived from factor analysis. Logistic regression analysis was used to assess the relationship between extracted profiles with CUD and its symptoms.

Results

CUD, bothersome postprandial fullness, early satiation, and epigastric pain or burning was identified in 723 (15.2%), 384 (8.1%), 302 (6.3%), and 371 (7.8%) of the study population. The frequency of all 31 somatic complaints was significantly higher in patients with CUD compared with controls ($P < 0.001$), and the most frequent was severe fatigue (45.1%). The profiles of somatic complaints were extracted in 4 domains, including "psychological", "gastrointestinal", "neuro-skeletal", and "pharyngeal-respiratory". The psychological (OR, 1.49; 95% CI, 1.44-1.54), gastrointestinal (OR, 2.22; 95% CI, 2.09-2.37), neuro-skeletal (OR, 1.52; 95% CI, 1.44-1.59), and pharyngeal-respiratory (OR, 2.09; 95% CI, 1.94-2.25) profiles were significantly associated with greater odds of CUD.

Conclusions

CUD and its symptoms are strongly associated with higher levels of somatic complaints and their related extracted profiles. This perhaps explains that why it can be difficult to treat, however further prospective investigations are required to confirm these associations.
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Key Words

Dyspepsia; Gastrointestinal diseases; Mental disorders; Psychosomatic disorders

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Introduction

Functional dyspepsia (FD) is one of the highly prevalent gastrointestinal (GI) disorders which is defined by the presence of symptoms originating from the gastroduodenal region, without identifiable cause by conventional diagnostic means.[1-4] Under the Rome III criteria, the FD symptoms include postprandial fullness, early satiation, epigastric pain or burning.[5] In addition, other symptoms may coexist, such as bloating (may be derived from the bowel), nausea (often of central origin), vomiting, belching, and heartburn (esophageal origin).[4,6,7] The dyspeptic symptoms reduce substantially the quality of life and greatly increase health costs.[8-12] Epidemiological studies reported a considerably high range of FD prevalence over the world. The prevalence of FD has been estimated to be 20-30% in the general population,[13] 8-23% and 20-30% in Asian and Western populations, respectively[2,5,14,15] and 8.9% in Iran.[16]

The etiology of FD is incompletely understood and it is believed to be multi-factorial.[17,18] Reported factors include gastric sensorimotor dysfunction, *Helicobacter pylori* infection, dysmotility, psychosocial factors (anxiety, anger–hostility, depression, and general psychological distress), and personality traits (among them, neuroticism).[17-23] In addition, somatization, which is characterized as physical bodily complaints not fully explained by organic reasons, plays an important role in functional GI disorders in general and in FD in particular.[23-26] Some studies indicated that there is a considerable overlap of somatic complaints like fatigue, headaches, sleep disorders, and abdominal discomfort in patients with FD, and that these are associated with epigastric pain, epigastric and retrosternal burning, and total dyspeptic symptom scores.[25,27,28] Despite several studies that reported high levels of somatization among patients with FD,[18,23,28-30] few have examined the frequency of somatization varies between FD patients and healthy counterparts.[18] In addition, to our knowledge, there is no data concerning the association of specific somatic complaint profiles with FD and its symptoms.

This highlights the need for a comprehensive study on examining the relationship between chronic uninvestigated dyspepsia (CUD) and its symptoms with somatic complaints. We have therefore examined this issue in a large group of patients with Rome III-defined CUD, and a control group of participants without CUD. We postulated that the frequency of somatic complaints would be greater in those with CUD than controls, and higher levels of somatic complaints profiles would be associated with greater odds of CUD and its symptoms.

Materials and Methods

Study Design and Participants

This cross-sectional study was conducted in the framework of the Study on the Epidemiology of Psychological, Alimentary Health and Nutrition (SEPAHAN) project that was performed in 2 phases in a large sample of Iranian population adults in the Isfahan province.[31] In the first phase of SEPAHAN, which included different questionnaires on demographic information, lifestyle, and nutritional factors, among 10 087 persons invited to participate, 8691 subjects took part (response rate: 86.16%). After this phase, the second wave of questionnaires which was designed to gather information on GI and psychological profiles, somatic complaints and personality traits questionnaires of participants were distributed, and 6239 completed questionnaires were returned to the main office of the project (response rate: 64.64%). Then, national identification numbers of the subjects were used to link the questionnaires from both waves. We collected and matched the information from both phases and after considering missing data, data on 4763 subjects with completed information was used in the current analysis. Fourteen questionnaires were used in the SEPAHAN project, among them, according to the objective of the current study, 8 questionnaires were considered. Informed consent was obtained from all subjects. The Bioethics Committee of the Isfahan University of Medical Sciences, Isfahan, Iran, approved the study (IUMS) (Project No. 189069, 189082, and 189086).

Procedures and Assessment of Variables

Assessment of chronic uninvestigated dyspepsia

In this study, a modified Persian version of the Rome III questionnaire was used for the assessment of functional GI disorders, including CUD. Face validation of this questionnaire indicated that most participants could not discriminate the difference between the descriptors (the rating scales) used in the original Rome III questionnaire (never, less than one day a month, one day a month, 2 to 3 days a month, one day a week, more than one day a week, and every day). Therefore, rating scales were modified to 4 descriptors (ie, never or rarely, sometimes, often, always) for each question.[32] In the current study, CUD was recognized having one or more of the following characteristics: bothersome postprandial fullness (defined as feeling uncomfortably full after a regular-sized meal, often or always), early satiation (defined as being unable to finish

a regular-sized meal, often or always), and/or epigastric pain or epigastric burning (defined as feeling pain or burning in the middle of abdomen, often or always). The validity of the Persian version of the Rome III questionnaire in an Iranian population has been determined previously.[16] Controls were all other participants who did not meet the Rome III criteria for CUD.

Assessment of somatization

In the SEPAHAN project, there is not separate questionnaire to assess somatic complaints, however, we found 31 common items among questions contained in SEPAHAN's questionnaires with the 47-items questionnaire used in the Lacourt et al's study[33] and the patient health questionnaire (PHQ),[34-37] as standard tools for the assessment of somatic complaints, and therefore we established a 31-item validated questionnaire. This was used to evaluate the frequency of somatic complaints. Respondents could indicate how much they had experienced each symptom in the past three months on a 4-point Likert scale (1 = never, sometimes, often, always). For one item (ie, dry mouth), the rating scale was as: never, low and high. We conducted a separate mini survey of 100 participants selected randomly in order to assess the reliability of this instrument. There was strong internal reliability, with a Cronbach's alpha score of 0.903.

Assessment of other variables

Self-administered standard questionnaires were distributed to collect information on age (years), gender (male/female), marital status (married, single), self-reported weight (kg), and height (cm). Body mass index (BMI) was calculated by dividing the weight in kilograms by height in meters squared. Educational attainments categorized into 3 categories as lower than diploma (12 years' formal education), diploma, and higher than diploma (including bachelor, master, and doctorate). An Iranian validated self-administered, Hospital Anxiety and Depression Scale (HADS) questionnaire was used to assess anxiety and depression.[38] It consisted of 14 items of which 7 are allocated to anxiety. It was answered using a 4-point Likert scale ranging from 0 (not present) to 3 (considerable). The anxiety score of participants could be between 0 and 21 points (0-7 normal, 8-21 mild, moderate or severe disorder). Psychological distress was measured by an Iranian validated self-administered questionnaire ie, a 12-item general health questionnaire (GHQ-12).[39] A participant's score could be between 0 and 12 points, and a threshold score of 4 or more was used to identify a participant with high-distress level.[40] The stressful life event (SLE) questionnaire was used to determine the intensity of perceived stress of subjects.

SLE consisted eleven domains, including home life, financial problems, social relations, personal conflicts, job conflicts, educational concerns, job security, loss and separation, sexual life, daily life, and health concerns. The validity of the questionnaire has been evaluated in a large sample of Iranian adults with Cronbach's α = 92% and acceptable correlation among SLE domains and SLE with GHQ-12.[41] The Neuroticism-Extraversion-Openness Five-Factor Inventory (NEO-FFI) was used to determine personality traits of subjects. The NEO-FFI results in a profile of the personality of the subject and consisted of 60 self-descriptive statements (a 5-point Likert-type scale including 0 = strongly disagree, 4 = strongly agree) about the personality that measured five dimensions of the normal personality (ie, neuroticism, extraversion, openness, agreeableness, and conscientiousness).[42] General practice physical activity questionnaire (GPPAQ) was used to assess an individual's current physical activity status. The GPPAQ consists of work and leisure time physical activity. It generates a simple, 4-levels physical activity index categorizing subjects as: active, moderately active, moderately inactive, and inactive.[43] In the current analysis, participants were classified into 2 categories ie, inactive (including inactive and moderately inactive) and active (including moderately active and active) as indicated earlier.

Statistical Methods

Continuous and categorical variables were represented as mean (SE) and frequency (percentage), respectively. To compare the continuous variables between patients with CUD and controls, Independent Student's t test was conducted. Distribution of study participants in terms of categorical variables and the number with the levels of "often and always" of the 31 individual somatic complaints was compared between those with CUD and controls using the Chi-square test.

Profiles of somatic complaints were extracted using factor analysis based on the principal component extraction approach on the 31 individual somatic complaints. The orthogonal varimax rotation procedure was used to find the interpretable factors. Factors were retained for further analysis based on their natural interpretation and eigenvalues on the scree plot. In this study, we retained factors with eigenvalues > 2 as this cutoff could result in more interpretable somatic complaints profiles and explain sufficient amounts of overall variation. Four main somatic complaints profiles were labeled based on the loaded somatic complaints in each factor. The factor score for each profile was computed by summing up items of somatic complaints weighted by their factor loadings and assigned to each participant.

To assess the relationship between extracted factors of somatic complaints and CUD, logistic regression analysis was performed in different models. Also, to assess the association between profiles of somatic complaints, as the main independent variables, and fre- quency (never, sometimes, often, and always) of symptoms of CUD (bothersome postprandial fullness, early satiation, and epigastric pain or burning) as the outcome variables, we applied proportional odds ordinal logistic regression. Adjusted ORs with 95% CI for

Table 1. Demographic, Life Style, and Psychological Characteristics of Study Participants

Characteristics	CUD (n = 723)	Control (n = 4040)	P-value[a]
Demographic characteristics			
Age (yr)	36.17 ± 0.32	36.65 ± 0.14	0.174
Females	457 (63.2)	2200 (54.5)	< 0.001
Marital status			0.748
Married	578 (81.6)	3198 (81.1)	
Single	130 (18.4)	744 (18.9)	
Educational Level			< 0.001
Under Diploma (< 12 yr)	132 (18.8)	506 (12.9)	
Diploma (12 years)	233 (33.1)	1115 (28.3)	
University Graduate (> 12 yr)	338 (48.1)	2312 (58.8)	
Life style			
BMI	24.61 ± 0.18	25.04 ± 0.06	0.022
Physical activity			< 0.001
Inactive and moderately inactive	496 (72.4)	2359 (63.9)	
Moderately active and active	189 (27.6)	1333 (36.1)	
Psychological characteristics			
Psychological distress			< 0.001
No	404 (57.1)	3157 (80.5)	
Yes	304 (42.9)	763 (19.5)	
Anxiety			< 0.001
No	458 (64.5)	3545 (89.8)	
Borderline	128 (18.0)	257 (6.5)	
Yes	124 (17.5)	145 (3.7)	
Depression			< 0.001
No	327 (46.0)	2988 (75.8)	
Borderline	202 (28.4)	653 (16.6)	
Yes	182 (25.6)	301 (7.6)	
Intensity of perceived stress			< 0.001
No at risk	110 (15.2)	1315 (32.5)	
At risk	613 (84.8)	2725 (67.5)	
Personality traits			
Neuroticism score	22.69 ± 0.29	18.02 ± 0.12	< 0.001
Extraversion score	26.68 ± 0.26	29.45 ± 0.11	< 0.001
Openness score	23.69 ± 0.20	24.11 ± 0.08	0.047
Agreeableness score	29.50 ± 0.24	31.33 ± 0.10	< 0.001
Conscientiousness score	34.69 ± 0.27	36.55 ± 0.11	< 0.001
The chronic and acute diseases[b]			< 0.001
No	532 (73.6)	3453 (85.5)	
Yes	191 (26.4)	587 (14.5)	

[a]P-values from independent samples t test for continuous data and from Pearson χ^2 for categorical data.
[b]Experiencing at least one of the chronic and acute diseases including high blood cholesterol and triglycerides (lipid disorder), high blood pressure (hypertension), diabetes mellitus, asthma, gallstones, Crohn's disease, stroke, heart attack, heart failure, and cancer.
CUD, chronic uninvestigated dyspepsia; BMI, body mass index.
Values are mean ± SE and others are number (%).

CUD and its symptoms are presented in 4 different models. First, we adjusted for demographic variables including age, gender, marital status, and educational level. In the second model, further adjustments were made for lifestyle variables including BMI and physical activity. Additional adjustment was conducted for psychological disorders (anxiety, depression, and intensity of perceived stress) in the third model. Personality traits, including neuroticism, extraversion, openness, agreeableness, and conscientiousness were adjusted in the fourth model. During the fitting of ordinal logistic regression, the proportional odd assumption or parallel lines test was checked using the Chi-square test. Data analyses were performed using Statistical Package for Social Sciences version 15 (IBM Corp, Armonk, NY, USA). P-values less than 0.05 were considered statistically significant.

Results

CUD was found in 723 (15.2%) of the study samples. Symptoms of bothersome postprandial fullness, early satiation, and epigastric pain or burning were identified in 384 (8.1%), 302 (6.3%),

Table 2. Prevalence of Individual Somatic Complaints in Chronic Uninvestigated Dyspepsia Patients Compared with Controls

Somatic Complaints	CUD		Controls	
	Often	Always	Often	Always
Sleep disorder	186 (26.8)	63 (9.1)	345 (9.0)	69 (1.8)
Pounding heart	128 (18.1)	34 (4.8)	156 (3.9)	33 (0.8)
Feeling low on energy	197 (27.7)	117 (16.5)	498 (12.7)	181 (4.6)
Feeling like "butterflies" in the stomach	128 (18.2)	63 (9.0)	140 (3.6)	55 (1.4)
Difficulty concentrating	128 (18.2)	63 (9.0)	140 (3.6)	55 (1.4)
Disturbing thoughts	154 (21.8)	98 (13.9)	362 (9.2)	168 (4.3)
Dry mouth[a]	284 (40.1)	70 (9.9)	1113 (28.2)	99 (2.5)
Chest pain	133 (18.8)	19 (2.7)	90 (2.3)	10 (0.3)
Feeling of fullness	320 (44.9)	64 (9.0)	0 (0.0)	0 (0.0)
Nausea	74 (10.6)	29 (4.2)	44 (1.1)	9 (0.2)
Gastroesophageal reflux	53 (7.7)	21 (3.1)	27 (0.7)	6 (0.2)
Pain or discomfort in the abdomen	206 (29.4)	49 (7.0)	152 (3.9)	17 (0.4)
Constipation	143 (20.3)	62 (8.8)	272 (6.9)	44 (1.1)
Diarrhea	31 (4.4)	5 (0.7)	38 (1.0)	5 (0.1)
Bloating or swelling of the abdomen	209 (30.3)	101 (14.7)	280 (7.3)	66 (1.7)
Anal pain	49 (7.3)	13 (1.9)	62 (1.6)	7 (0.2)
Headache	224 (31.5)	67 (9.4)	502 (12.8)	84 (2.1)
Back pain	182 (25.7)	86 (12.2)	466 (11.9)	154 (3.9)
Pain in joints	170 (24.0)	100 (14.1)	341 (8.6)	139 (3.5)
Eyesore	107 (15.2)	37 (5.3)	202 (5.1)	40 (1.0)
Severe fatigue	320 (45.1)	118 (16.6)	810 (20.6)	164 (4.2)
Dizziness and confusion	123 (17.3)	40 (5.6)	171 (4.3)	23 (0.6)
Chills and extreme cold	58 (8.2)	10 (1.4)	63 (1.6)	12 (0.3)
Hot flashes	95 (13.4)	25 (3.5)	132 (3.3)	25 (0.6)
Menstrual disorder[b]	94 (21.8)	45 (10.4)	238 (11.3)	132 (6.3)
Neck pain	75 (10.6)	13 (1.8)	88 (2.2)	17 (0.4)
Globus sensation	63 (8.9)	17 (2.4)	50 (1.3)	11 (0.3)
Having trouble swallowing	31 (4.3)	3 (0.4)	20 (0.5)	2 (0.1)
Shortness of breath	96 (13.6)	41 (5.8)	111 (2.8)	30 (0.8)
Hoarseness	40 (5.7)	5 (0.7)	33 (0.8)	11 (0.3)
Wheezing (asthma)	28 (4.0)	14 (2.0)	49 (1.2)	9 (0.2)

[a]The rating scale was as "never, low, and high."
[b]Female patients only.
Values are number (%).
P-value from Pearson χ^2. Distribution of all studied variables is significantly different between 2 groups at $P < 0.001$.

and 371 (7.8%) of subjects, respectively. The mean age was 36.17 ± 0.32 years in patients with CUD. Distribution of demographic, life style, psychological characteristics, and personality traits of study participants are summarized in Table 1. Patients with CUD were female predominant (63.2%), and they had lower levels of physical activities than controls ($P < 0.001$). Also, patients with CUD had higher anxiety, depression, psychological distress, intensity of perceived stress, and neuroticism scores ($P < 0.001$) while they had lower BMI, extraversion, openness, agreeableness, and conscientiousness scores ($P < 0.05$). The prevalence of experiencing at least one of the chronic and acute diseases including "high blood cholesterol and triglycerides (lipid disorder), high blood pressure (hypertension), diabetes mellitus, asthma, gallstones, Crohn's disease, stroke, heart attack, heart failure, and cancer" was significantly higher in patients with CUD (26.4%) compared with controls (14.5%) ($P < 0.001$) (Table 1).

Prevalence of Somatic Complaints Among Chronic Uninvestigated Dyspepsia Patients and Controls

The prevalence of the somatic complaints among patients with CUD and controls is presented in Table 2. The majority of symptoms had a 4-point Likert scale; we only reported the response of

Table 3. Factor Loadings for the 4 Extracted Somatic Complaints Profiles from 31 Somatic Complaints

Somatic complaints	Factor loadings[a]			
	Psychological	Gastrointestinal	Neuro-skeletal	Pharyngeal-respiratory
Sleep disorder	0.420			
Pounding heart	0.577			
Feeling low on energy	0.565			
Feeling like "butterflies" in the stomach	0.869			
Difficulty concentrating	0.869			
Disturbing thoughts	0.664			
Dry mouth		0.248		
Chest pain		0.454		
Feeling of fullness		0.662		
Nausea		0.509		
Gastroesophageal reflux		0.544		
Pain or discomfort in the abdomen		0.678		
Constipation		0.512		
Diarrhea		0.374		
Bloating or swelling of the abdomen		0.644		
Anal pain		0.473		
Headache			0.547	
Back pain			0.661	
Pain in joints			0.612	
Eyesore			0.461	
Severe fatigue			0.646	
Dizziness and confusion			0.513	
Chills and extreme cold			0.435	
Hot flashes			0.350	
Menstrual disorder			0.389	
Neck pain				0.570
Globus sensation				0.510
Having trouble swallowing				0.596
Shortness of breath				0.492
Hoarseness				0.612
Wheezing (asthma)				0.567
Variance explained (%)	12.70	11.73	11.55	8.85
Cumulative variance	12.70	24.43	35.99	44.84

[a]Factor loadings < 0.2 are not shown for simplicity.

participants to "often and always" categories. patients with CUD reported all 31 somatic complaints at both levels significantly higher than controls ($P < 0.001$). In the "often" level, the commonest somatic complaints reported among patients with CUD were severe fatigue (45.1%), followed by feelings of fullness (44.9%) and headaches (31.5%). In the "always" category, the most frequent somatic complaints reported among patients with CUD were severe fatigue (16.6%), followed by feeling low on energy (16.5%), bloating or swelling of the abdomen (14.7%), pain in joints (14.1%) disturbing thoughts (13.9%), back pains (12.2%), and menstrual disorders (10.4%) (Table 2).

Extraction of Somatic Complaints Profiles Using Factor Analysis

Profiles of somatic complaints were extracted using factor analysis based on principal component extraction approach on the 31 individual somatic complaints. Thus, four factors were extracted and labeled based on value of loadings within each factor as "psychological," "gastrointestinal," "neuro-skeletal," and "pharyngeal-respiratory" (Table 3). The 4 factors accounted for 12.70%, 11.73%, 11.55%, and 8.85%, respectively, of the total variance.

Table 4. Crude and Adjusted Odds Ratio (95% Confidence Interval) for Association Between Somatic Complaints Profiles with Chronic Uninvestigated Dyspepsia and Its Symptoms

Dependent variables	Somatic complaints profiles			
	Psychological	Gastrointestinal	Neuro-skeletal	Pharyngeal-respiratory
Crude Model				
CUD	1.49 (1.44-1.54)	2.22 (2.09-2.37)	1.52 (1.44-1.59)	2.09 (1.94-2.25)
Bothersome postprandial fullness	1.47 (1.43-1.51)	3.00 (2.84-3.18)	1.52 (1.46-1.58)	2.12 (1.99-2.25)
Early satiation	1.36 (1.32-1.40)	1.65 (1.59-1.71)	1.42 (1.36-1.47)	1.90 (1.79-2.02)
Epigastric pain or burning	1.45 (1.41-1.50)	2.20 (2.10-2.30)	1.50 (1.44-1.59)	2.05 (1.93-2.17)
Model I				
CUD	1.47 (1.41-1.53)	2.23 (2.08-2.39)	1.50 (1.41-1.58)	2.01 (1.85-2.18)
Bothersome postprandial fullness	1.46 (1.42-1.51)	3.03 (2.84-3.22)	1.51 (1.44-1.57)	2.09 (1.95-2.23)
Early satiation	1.36 (1.32-1.40)	1.67 (1.60-1.74)	1.44 (1.37-1.50)	1.91 (1.78-2.04)
Epigastric pain or burning	1.44 (1.40-1.49)	2.16 (2.06-2.27)	1.48 (1.42-1.55)	2.04 (1.91-2.18)
Model II				
CUD	1.46 (1.40-1.52)	2.24 (2.08-2.41)	1.50 (1.41-1.60)	2.02 (1.85-2.21)
Bothersome postprandial fullness	1.46 (1.41-1.51)	3.09 (2.89-3.31)	1.51 (1.44-1.58)	2.12 (1.97-2.28)
Early satiation	1.38 (1.33-1.42)	1.73 (1.65-1.81)	1.49 (1.42-1.57)	2.02 (1.87-2.17)
Epigastric pain or burning	1.43 (1.38-1.48)	2.16 (2.05-2.27)	1.50 (1.43-1.60)	2.08 (1.94-2.24)
Model III				
CUD	1.56 (1.43-1.70)	2.20 (2.03-2.38)	1.36 (1.26-1.46)	1.69 (1.54-1.86)
Bothersome postprandial fullness	1.51 (1.41-1.61)	3.10 (2.88-3.34)	1.37 (1.30-1.45)	1.75 (1.62-1.89)
Early satiation	1.31 (1.23-1.41)	1.63 (1.55-1.72)	1.35 (1.27-1.43)	1.70 (1.56-1.84)
Epigastric pain or burning	1.56 (1.45-1.66)	2.13 (2.01-2.25)	1.38 (1.30-1.46)	1.75 (1.62-1.89)
Model IV				
CUD	1.57 (1.44-1.71)	2.21 (2.04-2.40)	1.36 (1.26-1.46)	1.69 (1.53-1.86)
Bothersome postprandial fullness	1.52 (1.42-1.63)	3.12 (2.90-3.36)	1.38 (1.30-1.46)	1.75 (1.62-1.89)
Early satiation	1.32 (1.23-1.42)	1.64 (1.55-1.73)	1.36 (1.28-1.44)	1.69 (1.56-1.84)
Epigastric pain or burning	1.56 (1.46-1.67)	2.13 (2.02-2.26)	1.38 (1.30-1.46)	1.75 (1.62-1.90)

CUD, chronic uninvestigated dyspepsia.
Model I: adjusted for age, gender, marital status, and educational level; Model II: adjusted for age, gender, marital status, educational level, body mass index (BMI), and physical activity; Model III: adjusted for age, gender, marital status, educational level, BMI, physical activity, and psychological disorders (anxiety, depression, and intensity of perceived stress); Model IV: adjusted for all variables in model III, personality traits (neuroticism, extraversion, openness, agreeableness, and conscientiousness) and chronic and acute diseases.
Values obtained from binary logistic regression for CUD and ordinal logistic regression for its symptoms.

Association Between Somatic Complaints Profiles with Chronic Uninvestigated Dyspepsia and Its Symptoms

Crude and adjusted OR and 95% CI for the association between somatic complaints profiles and CUD and its symptoms in the entire study population are presented in Table 4. Significant associations were found between all somatic complaint profiles with CUD and its symptoms in crude models and adjusted models. In the crude model and also after adjustment for demographic variables, BMI and physical activity, and the psychological profile was significantly associated with greater odds of CUD (OR, 1.46; 95% CI, 1.40-1.52). This association remained significant even after further controlling for psychological disorders (anxiety, depression, intensity of perceived stress) and personality traits (1.57; 1.44-1.71). Similar associations were found between the psychological profile and symptoms of CUD including bothersome postprandial fullness and epigastric pain or burning (nearly 1.5; 95% CI, 1.4-1.6 for last model). The psychological profile had significant association with symptom of early satiation too (1.32; 1.23-1.42). The GI profile was significantly associated with greater odds of CUD in the crude model and adjusted models (2.2; 2.0-2.4). In the crude model and also after adjustment for demographic variables, BMI, physical activity, psychological disorders, and personality traits, the GI profile was significantly associated with greater odds of bothersome postprandial fullness (3.12; 2.90-3.36). In all models, the GI profile was significantly associated with greater odds of early satiation (1.64; 1.55-1.73 for the last model) and epigastric pain or burning (2.1; 2.0-2.3). In the crude model and also after adjustment for demographic variables, BMI, and physical activity, the neuro-skeletal profile was significantly associated with greater odds of CUD (1.5; 1.4-1.6). This association remained significant even after further controlling for psychological disorders and personality traits (1.36; 1.26-1.46). Similar associations were found between the neuro-skeletal profile and symptoms of CUD including bothersome postprandial fullness and epigastric pain or burning (nearly 1.38; 1.30-1.46 for last model). The neuro-skeletal profile had significant association with symptom of early satiation too (1.36; 1.28-1.44). The pharyngeal-respiratory factor was significantly related to the increased risk of CUD in the crude model and also after adjustment for demographic variables, BMI, and physical activity (2.0; 1.9-2.2). This association remained significant even after further controlling for psychological disorders and personality traits (1.69; 1.53-1.86). Similar associations were found between the pharyngeal-respiratory profile with bothersome postprandial fullness and epigastric pain

or burning (1.75; 1.62-1.9). In the crude model, the pharyngeal-respiratory factor was significantly associated with greater odds of early satiation (1.90; 1.79-2.02). This association remained significant even after controlling for the effects of potential confounding variables (1.69; 1.56-1.84).

Discussion

This cross-sectional study among a large sample of Iranian adults demonstrated that patients with CUD had a significantly higher prevalence of all somatic complaints than controls. When assessing the relationship between somatic complaint profiles extracted from factor analysis and CUD and its symptoms, we found that the psychological, neuro-skeletal, and pharyngeal-respiratory profiles were significantly associated with greater odds of CUD, bothersome postprandial fullness, early satiation, and epigastric pain or burning symptoms. Our study also reconfirmed an expecting relationship between the GI profile with greater odds of CUD and its symptoms. All aforesaid associations were observed with and without taking potential confounders into account.

The majority of previous studies were restricted to investigation of the association between psychological factors and FD which include a few somatic complaints or an overall score of somatization.[23,29] To the best of our knowledge, our research is the first large epidemiological study on the evaluation of the associations of distinct profiles of somatic complaints identified by factor analysis and CUD and its symptoms. Some studies indicated that in FD, somatization correlates with epigastric pain, epigastric and retrosternal burning, and total dyspeptic symptom scores.[27,28] In the present study, not only the most important somatic complaints in groups with and without CUD were compared, but also the conducted factor analysis provided us the possibility for evaluating the effect of extracted common concepts ie, somatic profiles on CUD and its symptoms.

In the current study, the extracted psychological profile from somatic complaints was one of the most important determinants of CUD and its symptoms. Also, our study showed significantly higher anxiety, depression, psychological distress, intensity of perceived stress, and neuroticism score in patients with CUD, than controls. These findings are consistent with other previous studies.[19-22,44] For example, Norton et al[45] showed that participants suffering from functional dyspepsia showed significant differences in terms of anxiety and depression when compared with controls. The results of Filipović et al[21] also approved these facts. Review studies such as that of Barry and Dinan also confirmed the co-morbidities of anxi-

ety, depressive, somatoform disorders, and neuroticism in patients with functional dyspepsia.[19] These psychological problems are commonly seen in most digestive disorders so that in the study of Van Oudenhove et al,[46] anxiety, depression, and somatization were used as the most important variables on separating functional gastroduodenal disorders (FGD). The results of Faramarzi et al[20] in Iran revealed that psychological problems (depression and anxiety) were more prevalent in FD patients. Nan et al,[47] based on possible brain-gut interaction, indicated that psychological factors may not only be just considered as an effect of FD; but also they could be a result of dyspeptic symptoms. However, Vishnar et al[48] obtained rather contradictory results; the results showed that, except for anxiety, no significant association was found between the other disorders and non-ulcer dyspepsia. Also De la Roca-Chiapas et al[49] showed that depression was not outlined as a significant predictor of FD. High scores for neuroticism as well as an increased rate for somatization and social anxiety in FD patients was reported by Holtmann et al.[50]

We also found that the psychological profile was significantly associated with greater odds of bothersome postprandial fullness, early satiation, and epigastric pain. Among a few studies about the association between psychological and somatic complaints with symptoms of CUD, some have presented indications of independent associations between scores of dyspeptic symptoms, such as the postprandial distress syndrome, with overall psychopathological stress, and particularly, somatization and depression.[30]

The results of our study are not surprising: given the strong association between FD and psychiatric comorbidity, it seems likely that patients with more GI symptoms have also more severe psychologic symptoms. The best combination of dimensions for describing this psychosocial disturbance and its positive association with CUD are included: personality (anger reactivity—the tendency to react readily with anger—and neuroticism), chronic social stressor threat, poor emotional support, and increased age. This profile, which combines psychological, social, and biological elements, is prototypic of the most severe chronic stress scenario. This pathway could be considered a pathophysiological mechanism capable of explaining the difference in the severity of the psychological suffering.[13,23]

The current study showed a significantly higher prevalence of the GI somatic complaints among patients with CUD than controls, and positive associations were observed between CUD and its symptoms with GI profiles extracted from factor analysis approach. These findings are naturally expected because of the large overlap between gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), and FD, and often they coexist in the same patient. There is great overlap between FD and GERD-like symptoms[51]; and this overlap is greatest between nonerosive and functional heartburn and FD in which the clinical spectrum that extends from FD to nonerosive reflux disease may be present in up to 70% of GERD disease in the community.[52] This association might indicate a common pathophysiologic mechanism.[53] The high overlaps between FD and its symptoms with other upper and lower GI disorders, along with their strength interactions with psychopathological factors notably anxiety, depression, psychological distress and psychological somatization profile, can be viewed as the most important implication in this regard.[13,54]

We observed in the neuro-skeletal domain of psychosomatic symptoms that severe fatigue is the commonest reported somatic complaint among patients with CUD. Some previous studies showed that FD is one of the most prevalent functional gastrointestinal disorder (FGID) with a high comorbidity with other FGIDs such as IBS, as well as with non-GI functional somatic syndromes such as chronic fatigue syndrome. Approximately 40% of FD patients have comorbid chronic fatigue-like symptoms; (non-GI) somatic symptom level is associated with both FD and chronic fatigue comorbidity.[23]

In the study of Bennett et al,[29] a few items such as fatigue, unpleasant taste, dry skin or eczema, and binge eating habits were considered as somatic complaints, and were shown as predictive of the combination of FD and IBS in general.[29] In line with our study, in the aforesaid study, fatigue was most likely to be present in FD patients.[29] Gracie et al[18] showed that the commonest item reported among patients with FD was feeling tired or low in energy, followed by trouble sleeping, and back pain. Van Oudenhove et al[23] showed that dyspepsia symptom severity is associated with depression, fatigue, and somatization.[23] However, it should be noted that in the aforesaid study the somatization scores with no separate effects of each items or domains, were used; therefore it can only be considered as indicative of functional somatization. In our study, in line with Jiang et al's study,[55] the prevalence of sleeping disorders, as a somatic complaint, was significantly higher in patients with FD than healthy controls.[55] These findings strongly suggest that FD patients may be characterized by a generalized tendency to experience and report multiple somatic complaints. An important issue that remains to be elucidated is whether this tendency (often described as "somatization") needs to be conceptualized as a primary phenomenon ("functional somatization"), or rather as the result of a complex psychobiological process in which different psychological dimensions such as personality traits including neuroticism, anxiety, depression or negative affects lead to amplification of bodily signals, most likely through sensitization of pain-processing neural systems

(secondary phenomenon, "presenting somatization").[23,56-58]

Our study identified a somatic complaint profile that we named as the "pharyngeal-respiratory" factor. This somatic profile similar to other identified somatic complaints was positively associated with CUD and its symptoms. Also, the individual pharyngeal-respiratory symptoms assessed in our study were more prevalent in patients with CUD than control participants. These findings are strongly in line with the results of previous studies that have indicated significant association between upper GI disorders and respiratory symptoms and complications, in which high prevalence of respiratory disorders or symptoms such as asthma, chronic cough or hoarseness, wheezing, and shortness of breath have been indicated in these patients. These symptoms may be present singly or collectively and usually are assumed to be caused by irritation of the larynx and hypopharynx by gastric contents.[59,60]

It is important to recognize some strengths, as well as potential limitations of the present study. A major strength of our large sample epidemiological population based study is the application of the factor analysis technique to distinct profiles of somatic complaints, instead of considering them as a single complaint in their relationships with CUD and its symptoms. Furthermore, the mediating impact of various potential confounding variables such psychological problems, personality traits, physical activity, and demographic variables, in order to evaluate reliable associations between the main study variables, have been considered. Several limitations need to be considered when interpreting our findings. The limitation of the majority of questionnaires on evaluating somatic complaints as a self-report measure is that they cannot distinguish between "medically explained" and "unexplained" symptoms,[61] which is an important feature of the somatization concept.[24,62] Accordingly, it should be emphasized that the somatic complaints in our study can only be characterized as indicative of somatization. In this study, the investigated associations are restricted to CUD, not organic dyspepsia: accordingly, the observed results are generalized only to CUD. Due to the cross-sectional nature of the SEPAHAN design, we cannot infer cause–effect relationships from our findings; thus, to identify the real association between CUD and its symptoms and somatic complaints, further prospective cohort investigations are suggested. It should also be kept in mind, as a common problem of epidemiological studies, that all used information in the present analysis were collected by self-administered questionnaires, and this method of data collection might lead to misclassifying the participants. These misclassifications would attenuated the original associations. Accordingly, it seems that the observed associations in the current study are much stronger in reality. The subjective or arbitrary deci-

sions in factor analysis, such as the choice of somatic complaints to be included in the analysis, the number of factors to be extracted, and selecting the method of rotation should be considered while interpreting the results.[63] Finally, since the SEPAHAN study's participants were 20 to 50 years of age working in health centers and not academic staff members of the IUMS, they may have a healthier lifestyle. Thus, generalization of the present findings to the general population in Iran, as well as to other cultural backgrounds, must be done with caution.

In conclusion, patients with CUD had a higher frequency of somatic complaints than control participants. Patients with CUD reported a greater frequency of severe fatigue and feeling low on energy. Also, we found that CUD and its symptoms are strongly associated with higher levels of all four somatic complaints profiles identified by factor analysis, especially the psychological, neuroskeletal, and pharyngeal-respiratory profiles. Our study's findings, in the context of an observational study, provide primary evidence about the usefulness of treating somatic complaints for targeting CUD's treatment. Also, these findings could be an indication of the key role of psychological factors on CUD and its symptoms, and may explain why it can be difficult to treat. However, further prospective particularly interventional investigations are required to confirm the impacts of treating of somatic complaints on CUD.

Conflicts of interest: None.

Author contributions: Peyman Adibi, Awat Feizi, Ammar Hassanzadeh Keshteli, and Hamid Afshar contributed to the conception and design of the study, collection and assembly of the data; and Awat Feizi and Zahra Heidari contributed to the statistical analysis plan for the study, the analysis and interpretation of the data, and the drafting of the manuscript. All authors read and approved the final manuscript.

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